

New claim Set after Preliminary Amendment

1. A FLINT analog resistant to proteolysis at position 218 of SEQ ID NO:1 (alternatively, position 247 of SEQ ID NO:3), *in vivo* and/or *in vitro*.
2. A FLINT analog resistant to proteolysis at position 218 of SEQ ID NO:1 comprising an amino acid substitution in the region defined by amino acids 214 through 222 of SEQ ID NO:1, selected from the group consisting of:
 - a. Gly at position 214 is replaced by any naturally occurring amino acid other than Gly;
 - b. Pro at position 215 is replaced by any naturally occurring amino acid other than Pro;
 - c. Thr at position 216 is replaced by any naturally occurring amino acid other than Thr;
 - d. Pro at position 217 is replaced by any naturally occurring amino acid other than Pro;
 - e. Arg at position 218 is replaced by any naturally occurring amino acid other than Arg;
 - f. Ala at position 219 is replaced by any naturally occurring amino acid other than Ala;
 - g. Gly at position 220 is replaced by any naturally occurring amino acid other than Gly;
 - h. Arg at position 221 is replaced by any naturally occurring amino acid other than Arg;
 - i. Ala at position 222 is replaced by any naturally occurring amino acid other than Ala.
3. A FLINT analog as in Claim 2 comprising an amino acid substitution in the region defined by amino acids 214

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through 222 of SEQ ID NO:1, selected from the group consisting of:

- a. Gly at position 214 is replaced by a positively charged amino acid that is not Gly;
- b. Pro at position 215 is replaced by a positively charged amino acid that is not Pro;
- c. Thr at position 216 is replaced by a positively charged amino acid that is not Thr;
- d. Pro at position 217 is replaced by a positively charged amino acid that is not Pro;
- e. Arg at position 218 is replaced by a positively charged amino acid that is not Arg;
- f. Ala at position 219 is replaced by a positively charged amino acid that is not Ala;
- g. Gly at position 220 is replaced by a positively charged amino acid that is not Gly;
- h. Arg at position 221 is replaced by a positively charged amino acid that is not Arg; or
- i. Ala at position 222 is replaced by a positively charged amino acid that is not Ala.

4. A FLINT analog as in Claim 2 comprising an amino acid substitution in the region defined by amino acids 214 - 222 of SEQ ID NO:1, selected from the group consisting of:

- a. Gly at position 214 is replaced by a negatively charged amino acid that is not Gly;
- b. Pro at position 215 is replaced by a negatively charged amino acid that is not Pro;
- c. Thr at position 216 is replaced by a negatively charged amino acid that is not Thr;

- d. Pro at position 217 is replaced by a negatively charged amino acid that is not Pro;
- e. Arg at position 218 is replaced by a negatively charged amino acid that is not Arg;
- f. Ala at position 219 is replaced by a negatively charged amino acid that is not Ala;
- g. Gly at position 220 is replaced by a negatively charged amino acid that is not Gly;
- h. Arg at position 221 is replaced by a negatively charged amino acid that is not Arg; or
- i. Ala at position 222 is replaced by a negatively charged amino acid that is not Ala.

5. A FLINT analog as in Claim 2 comprising an amino acid substitution in the region defined by amino acids 214 - 222 of SEQ ID NO:1, selected from the group consisting of:

- a. Gly at position 214 is replaced by a polar uncharged amino acid that is not Gly;
- b. Pro at position 215 is replaced by a polar uncharged amino acid that is not Pro;
- c. Thr at position 216 is replaced by a polar uncharged amino acid that is not Thr;
- d. Pro at position 217 is replaced by a polar uncharged amino acid that is not Pro;
- e. Arg at position 218 is replaced by a polar uncharged amino acid that is not Arg;
- f. Ala at position 219 is replaced by a polar uncharged amino acid that is not Ala;
- g. Gly at position 220 is replaced by a polar uncharged amino acid that is not Gly;

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- h. Arg at position 221 is replaced by a polar uncharged amino acid that is not Arg; or
- i. Ala at position 222 is replaced by a polar uncharged amino acid that is not Ala.

6. A FLINT analog as in Claim 2 comprising an amino acid substitution in the region defined by amino acids 214 - 222 of SEQ ID NO:1, selected from the group consisting of:

- Gly at position 214 is replaced by a nonpolar amino acid that is not Gly;
- Pro at position 215 is replaced by a nonpolar amino acid that is not Pro;
- Thr at position 216 is replaced by a nonpolar amino acid that is not Thr;
- Pro at position 217 is replaced by a nonpolar amino acid that is not Pro;
- Arg at position 218 is replaced by a nonpolar amino acid that is not Arg;
- Ala at position 219 is replaced by a nonpolar amino acid that is not Ala;
- Gly at position 220 is replaced by a nonpolar amino acid that is not Gly;
- Arg at position 221 is replaced by a nonpolar amino acid that is not Arg; or
- Ala at position 222 is replaced by a nonpolar amino acid that is not Ala.

7. A FLINT analog resistant to proteolysis at position 218 of SEQ ID NO:1 comprising an amino acid substitution in SEQ ID NO:1, selected from the group consisting of:

- a.Arg at position 218 is replaced by Gln;

- b. Arg at position 218 is replaced by Glu;
- c. Thr at position 216 is replaced by Pro;
- d. Arg at position 218 is replaced by Ala;
- e. Arg at position 218 is replaced by Gly;
- f. Arg at position 218 is replaced by Ser;
- g. Arg at position 218 is replaced by Val
- h. Arg at position 218 is replaced by Tyr;
- i. Arg at position 218 is replaced by Asn; and
- j. Pro at position 217 is replaced by Tyr.

8. A FLINT analog as in Claim 1 wherein Arg at position 34 of SEQ ID NO:1 is replaced by Asn, Asp at position 36 is replaced by Thr, and Arg at position 218 is replaced by an amino acid selected from the group consisting of:

- a. any naturally occurring amino acid that is not Arg;
- b. any positively charged amino acid that is not Arg;
- c. any negatively charged amino acid that is not Arg;
- d. any polar uncharged amino acid that is not Arg;
- e. any nonpolar amino acid that is not Arg; and
- f. an amino acid that is Glu, Gln, Asn, Ala, Gly, Ser, Val, or Tyr.

9. A FLINT analog as in Claim 1 wherein Arg at position 34 of SEQ ID NO:1 is replaced by Asn, Asp at position 36 is replaced by Thr, Asp at position 194 is replaced by Asn, Ser at position 196 is replaced by Thr, and Arg at position 218 is replaced by an amino acid selected from the group consisting of:

- a. any naturally occurring amino acid that is not Arg;
- b. any positively charged amino acid that is not Arg;

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- c. any negatively charged amino acid that is not Arg;
- d. any polar uncharged amino acid that is not Arg;
- e. any nonpolar amino acid that is not Arg; and
- f. an amino acid that is Glu, Gln, Ala, Gly, Ser, Val, or Tyr.

10. A FLINT analog as in Claim 1 wherein Ser at position 132 of SEQ ID NO:1 is replaced by Asn, and Arg at position 218 is replaced by an amino acid selected from the group consisting of:

- a. any naturally occurring amino acid that is not Arg;
- b. any positively charged amino acid that is not Arg;
- c. any negatively charged amino acid that is not Arg;
- d. any polar uncharged amino acid that is not Arg;
- e. any nonpolar amino acid that is not Arg; and
- f. an amino acid that is Glu, Gln, Ala, Gly, Ser, Val, or Tyr.

12. A FLINT analog as in Claim 1 wherein Arg at position 34 of SEQ ID NO:1 is replaced by Asn, Asp at position 36 is replaced by Thr, Asp at position 194 is replaced by Asn, Ser at position 196 is replaced by Thr, and Arg at position 218 is replaced by Gln.

13. A FLINT analog as in Claim 1 wherein Thr at position 216 of SEQ ID NO:1 is replaced by Pro, and Arg at position 218 is replaced by Gln.

14. A method to treat or prevent a disease or condition in a mammal comprising the administration of a

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therapeutically-effective amount of a protease resistant FLINT analog of Claim 2.

15. A method as in Claim 14 wherein said disease or condition is acute lung injury, acute respiratory distress syndrome, or ulcerative colitis.

16. A pharmaceutical formulation comprising as an active ingredient a protease resistant FLINT analog of Claim 2 associated with one or more pharmaceutically acceptable carriers, excipients, or diluents thereof.

21. A FLINT analog resistant to proteolysis at position 218 of SEQ ID NO:1 comprising the amino acid sequence of SEQ ID NO:1, wherein Arg at position 218 is substituted by Gln.

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